Expert consensus recommendations for improving and standardising the assessment of patients with generalised myasthenia gravis

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Introduction

- Generalised myasthenia gravis (gMG) is a rare and chronic, immunoglobulin G (IgG)-mediated, neuromuscular autoimmune disease, which causes debilitating and potentially life-threatening muscle weakness[1,2]
- Clinical symptoms of gMG may vary and fluctuate over time, and symptom assessments are infrequent or inconsistent, making the evaluation of symptom state and disease burden difficult[1–6]
- Regular and consistent disease assessment could improve patient care; however, the use of assessment tools in clinical practice lacks standardisation[5–7]
- A gMG expert panel convened to propose evidence- and expert-derived guidance on patient assessment

Methods

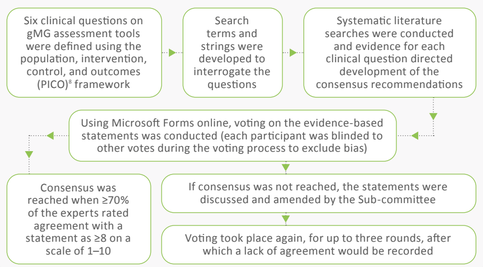
- A European expert panel, consisting of 21 experienced gMG neurologists from eight European countries (Belgium, Denmark, France, Germany, Italy, Poland, Spain and UK), was formed
- Four of the experts formed a Sub-committee to lead this consensus study and a further 11 contributed to the development of the recommendations

A modified Delphi approach was taken to review current evidence on assessment tool use in gMG and develop expert-derived consensus recommendations for good practice (Fig. 1)

The Sub-committee identified six key areas where improvement and standardisation in the assessment of patients with gMG could improve outcomes:

1. Assessment of disease burden
2. Assessment of depression, anxiety and fatigue
3. Domains not currently assessed by tools
4. Clinically meaningful assessment thresholds
5. Assessment of treatment-related burden
6. Assessments supporting treatment decisions

Fig. 1. Overview of the literature search and evidence-based statement development process



Results

- The modified-Delphi approach generated 18 consensus statements, across the six clinical questions, which were sent to the 21 members of the expert panel for voting
- In round one of voting (open for 4 weeks), consensus was reached for 16 of the 18 statements, with responses from 15 members
- During the second round of voting (open for 5 weeks), consensus was reached on the two amended statements

1. Assessment of disease burden

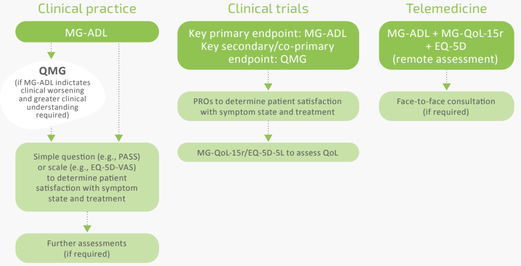
Question: What are the optimal tools/combination of tools, and optimal frequency, for understanding gMG disease burden in a) clinical practice, b) a clinical trial/research setting, and c) a telemedicine setting?

Consensus statements	Consensus, % (n/N)
Clinical practice	
Consistent use of the MG-ADL scale should be applied in clinical practice to understand gMG disease burden; if the MG-ADL indicates worsening gMG, the QMG scale can be used to provide greater clinical understanding and support onward decisions	93.3 (14/15)
It is advised that an additional scale should follow the MG-ADL in clinical practice to determine patient satisfaction with symptom state and treatment; the MG-QoL-15r, PASS or EQ-5D-VAS can be used effectively in this setting	93.3* (14/15)
In clinical practice, should patients be dissatisfied with their symptom state or treatment, additional outcomes should be explored, such as quality of life, psychological/emotional burden or fatigue, with appropriate assessments	100 (15/15)
Timing of gMG assessments should reflect the patient's symptom state (i.e., less frequent for stable *vs* fluctuating symptoms) and guidance for continuing, stopping retreatment or repeating treatment, should be based on clinical evaluation	100 (15/15)
Clinical research	
The MG-ADL is recommended as the primary endpoint in clinical trials, with the QMG as a co-primary or key secondary endpoint	93.3 (14/15)
PROs are recommended to be included for the assessment of patient satisfaction with symptom state and treatment in the clinical trial setting	93.3 (14/15)
The MG-QoL-15r or EQ-5D-5L may be used to measure quality of life in clinical trial settings	100 (15/15)
Telemedicine	
In telemedicine settings, MG-ADL should be used to assess disease severity, and combined with EQ-5D and MG-QoL-15r to assess QoL; the combined results can determine the need and urgency for a face-to-face consultation	93.3 (14/15)
Timing of gMG assessments should reflect the patient's symptom state (i.e., less frequent for stable *vs* fluctuating symptoms) and guidance for continuing, stopping retreatment or repeating treatment, should be based on clinical evaluation	100 (15/15)

*Consensus reached after revision and second round of voting.

- Algorithms for disease burden assessment were developed based on the consensus recommendations for this question (Fig. 2)

Fig. 2. Algorithms for disease burden assessment based on consensus recommendations



2. Assessment of depression, anxiety and fatigue

Question: What are the general principles/recommendations for incorporating depression, anxiety, and fatigue scales in patient assessment?

Consensus statements	Consensus, % (n/N)
No specific scales are validated for measuring depression, anxiety and fatigue in the context of gMG at the current time. However, fatigue and fatigability may be measured effectively using the FSS, MFI-20 or Chalder fatigue scale; and depression and anxiety may be measured effectively using the PHQ, HADS or MDI	80 (12/15)
Comorbidity assessment should include the relevant multidisciplinary team member, such as a psychiatrist for anxiety or depression	86.7 (13/15)

3. Domains not currently assessed by tools

Question: Are there any patient assessment domains (i.e., outcomes or symptoms) that should be captured to assess disease status, but are currently not included in any existing gMG patient assessment tools?

Consensus statements	Consensus, % (n/N)
There is a need for physician- and patient-administered assessment tools to better understand the practical, psychosocial impact of gMG and its treatment on patients, their families and caregivers	100 (15/15)
Although current evidence does not support the use of a specific scale over others to assess fatigability, measures such as the MFI-20 and Chalder Fatigue scales should be used more consistently to assess the burden and impact of this important symptom in patients with gMG	73.3 (11/15)
Ocular item sub-scores of gMG assessments should be reviewed with careful attention to evaluate specific ocular symptoms in patients	93.3* (14/15)

*Consensus reached after revision and second round of voting.

4. Clinically meaningful assessment thresholds

Question: What are the thresholds for minimally important/clinically meaningful differences in assessment scores in gMG within clinical practice?

Consensus statements	Consensus, % (n/N)
At the current time it is not possible to make recommendations on absolute thresholds for minimally-important and clinically-meaningful differences in gMG scores as these are heavily dependent on the patient's experience and should be considered relative to baseline assessment scores	100 (15/15)
Use of a patient satisfaction scale, such as the PASS or a symptom satisfaction questionnaire, can give an indication of whether changes in symptom state as assessed by a clinician, with a scale such as the MG-ADL, correspond to meaningful changes from the patient's perspective	86.7 (13/15)

5. Assessment of treatment-related burden

Question: How should treatment-related burden be assessed in patients with gMG in clinical practice?

Consensus statement	Consensus, % (n/N)
There are currently no appropriate scales to measure the adverse event, psychological or practical burden associated with gMG treatment, or to differentiate treatment-related adverse events from gMG-related symptoms; however, treatment-related adverse event burden can be assessed through longitudinal measurement of objective parameters, such as frequency, and the use of toxicity indices in conjunction with MG-specific assessments of MG burden	80 (12/15)

6. Assessments supporting treatment decisions

Question: How do current gMG assessments support decisions around re-treatment or escalation of treatment, and which tools can optimally inform treatment decisions?

Consensus statement	Consensus, % (n/N)
Multiple disease, patient and treatment-related factors, including the patient's preferences, need to be considered when defining treatment goals and making therapeutic decisions in gMG; therefore, a general recommendation on how to decide upon re-treatment or treatment escalation is not appropriate	86.7 (13/15)

Key Takeaways

- We strongly advised that the MG-ADL is used consistently across all clinical settings
  - The MG-ADL is a reliable patient-reported scale that can be used at various stages of a patient's gMG disease journey to give a good indication of gMG improvement or worsening,[9] and can be followed by other assessments when further evaluation is warranted
- The PASS or similar assessment should follow the MG-ADL to determine patient satisfaction with symptom state and treatment
- Fluctuations in MG-ADL scores can swiftly highlight the need for a QMG or QoL assessment
- Timing and frequency of gMG assessments should be consistent and reflect the patient's symptom state such that individuals with fluctuating symptoms have more frequent assessment than patients with stable disease

Conclusions

The Sub-committee was able to reach a consensus on all 18 statements explored and concluded that it is critical to consistently incorporate subjective and objective measures of gMG severity and disease burden across the continuum of care to improve outcomes for patients

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Abbreviations

EQ-5D, EuroQoL five dimensions; **EQ-5D-5L**, five-level EuroQoL five dimensions; **FSS**, Fatigue Severity Scale; **gMG**, generalised myasthenia gravis; **HADS**, Hospital Anxiety and Depression Scale; **IgG**, immunoglobulin G; **MDI**, Multiscale Depression Inventory; **MFI-20**, Multidimensional Fatigue Inventory-20; **MG**, myasthenia gravis; **MG-ADL**, Myasthenia Gravis Activities of Daily Living score; **MG-QoL-15r**, Revised Myasthenia Gravis Quality of Life 15-item score; **QMG**, Quantitative Myasthenia Gravis score; **QoL**, quality of life; **PASS**, patient acceptable symptom state; **PICO**, population, intervention, control, outcomes; **PHQ**, Patient Health Questionnaire; **PROs**, patient reported outcomes; **VAS**, visual analogue scale.

Conflicts of interest

Andrea Meisel is an advisor, consultant, investigator and/or speaker and has received grants (paid to institution) and honoraria from Alexion, argenx, Axunio, Grifols, Hormosan, Janssen, Merck, Octapharma and UCB. He serves as chairman of the medical advisory board of the German Myasthenia Gravis Society.
Francesco Saccà received public speaking honoraria from Alexion, argenx, Biogen, Mylan, Novartis, Roche, Sanofi and Teva; he also received compensation for advisory boards or consultation fees from Alexion, Almirall, argenx, Axexis, Biogen, Forward Pharma, Lexeo Therapeutics, Merk, Novartis, Novatek, Reata, Roche, Sanofi and Takeda; he is principal investigator in clinical trials for Alexion, argenx, Immunovant, Novartis, Prilenia and Sanofi.
Jennifer Spillane has received compensation for advisory boards and travel compensation from argenx and UCB and has received public speaking honoraria for argenx.
John Vissing has acted as advisory board consultant or speaker for Amicus Therapeutics, argenx BVBA, Arvinas, Atamyo Therapeutics, Biogen, Dyne Therapeutics, Fulcrum Therapeutics, Horizon Therapeutics, Lupin, ML Biopharma, Novartis Pharma AG, Regeneron, Roche, Sanofi Genzyme, Sarepta Therapeutics, UCB Biopharma SPRL and Zogenix, and received research grants, travel support and/or speaker fees from Alexion, AstraZeneca Rare Disease, Edgewise Therapeutics, Fulcrum Therapeutics, Sanofi Genzyme and UCB Biopharma SPRL.
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